Specialty Reviews – Biologics

CDER Forum for International Regulators

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Outline

- Biological Products
  - Highlights in history
  - What is a biologic?
  - How are biologics different?
  - Biologics in CDER
- Regulation of Biologics
  - Comparison to drugs
  - Licensing
  - Post-approval
  - NDA and BLA similarities & differences
  - CDER review structure

CDER Forum for International Drug Regulatory Authorities

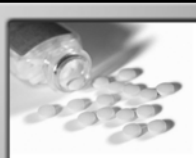
The Bad Beginning

- Early 1900 - anti-sera, etc. for epidemics of cholera, typhoid, diphtheria, etc.
- Limited understanding of manufacturing processes that affect purity/potency

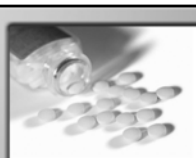
- DISASTER #1
  - Diphtheria epidemic of 1901
  - Antitoxin resulted in deaths of 10 children, produced from a horse ("Jim") that had contracted tetanus
  - 'anyone with some technical knowledge and a stable of horses'

Disasters and Laws

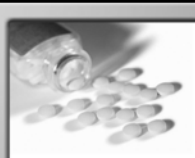
- Drugs
  - 1906 Pure Food and Drug Act
  - 1937 Elixir of Sulfanilamide (with diethylene glycol)
  - 1938 FFD&C Act
  - 1962 Thalidomide
  - 1962 Kefauver-Harris amendment (effectiveness standard)
  - 1983 FDA Center for Drugs and Biologics
  - 1988 CDER
- Biologics
  - 1901 Diptheria antitoxin (tetanus)
  - 1902 Biologics Control Act
    - Treasury Dept.
    - PHS Hygienic Lab.
    - renamed NIH (1930)
    - NIH Div. of Biologics Control (1937)
  - 1944 Public Health Service (PHS) Act
  - 1955 improperly inactivated polio vaccine
    - NIH Div. of Biological Standards
    - 1972 FDA Bureau of Biologics
  - 1983 FDA Center for Drugs and Biologics
  - 1988 CBER
  - 2003 Therapeutic Biological products transferred to CDER



Diphtheria annual incidence and mortality ratios in US, 1920-1975 (From CDC)

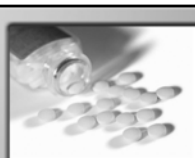


What is a Biologic?



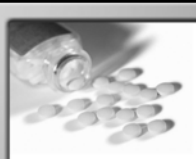
Section 351 PHS Act
(as amended by FDAMA)

- "Biological Product" – a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings."



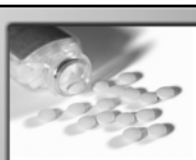
The Regulations Give More Detail

- For example, from 21 CFR 600.3(h):
  - A product is analogous to a therapeutic serum, if composed of whole blood or plasma or containing some organic constituent or product other than a hormone or an amino acid, derived from whole blood, plasma, or serum.



CBER/CDER Intercenter Agreement

- Biological products subject to licensure:
  - Vaccines, regardless of method of manufacture….
  - in vivo diagnostic allergenic products… intended for therapeutic use as "hyposensitization" agents
  - Human blood or human blood-derived products …, animal-derived procoagulant products and animal or cell culture-derived hemoglobin-based products intended to act as red blood cell substitutes
  - Immunoglobulin products, whether monoclonal or polyclonal, produced in humans, animals or in cell culture



CBER/CDER Intercenter Agreement (cont.)

- Products composed of or intended to contain intact cells or intact microorganisms including bacteria, fungi, viruses or virus pseudotypes, or viral vectors
- Protein, peptide or carbohydrate products produced by cell culture *excepting antibiotics, hormones*…, and products previously derived from human or animal tissue and regulated as approved drugs
- Protein products produced in animal body fluids by genetic alteration of the animal, i.e., transgenic animals
- Animal venoms or constituents of venoms.

CBER/CDER
Intercenter Agreement: Exceptions

- CDER is responsible for:
  - Hormone products, regardless of method of manufacturing, e.g., insulin, human growth hormone, pituitary hormones.

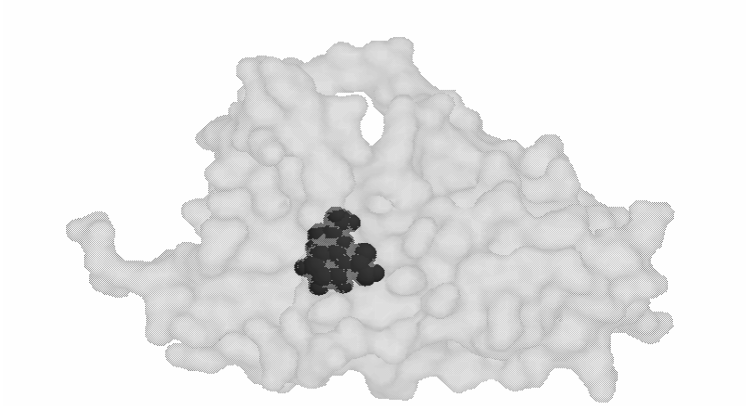
How are Biotechnology Products Different?

BIG

COMPLEX

DIVERSE

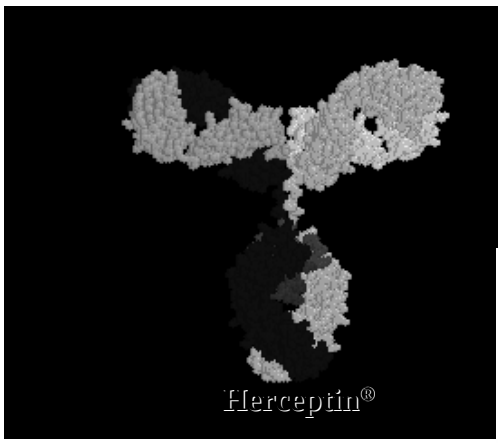
A chemically based compound like Acetylsalicylic acid (Aspirin) shown in red is small and not very complex when compared to EPO. Aspirin (Red) has been placed on top of the surface of EPO (Cyan) as a comparison.



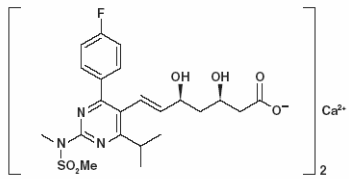
EPO is a large molecule with more than 1000 atoms as represented by the Space Filling model

The more than 1000 atoms of EPO make a complex surface which interacts with the receptor (green) in a very specific way

Relative size



20 Å



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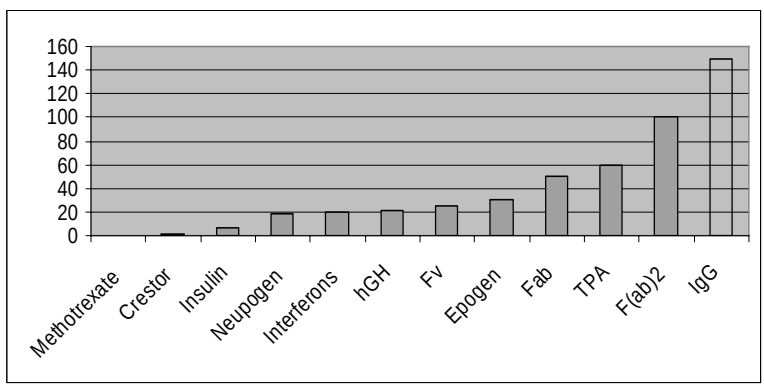
Comparative M.W.s of Biotechnology Drugs



CDER Forum for International Drug Regulatory Authorities

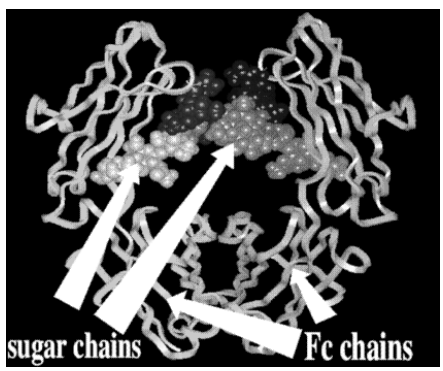
Biologics vs. Drugs

- Biologic products generally more complex
  - Many innovative products
    - virtually every new biologic is a novel product (NME)
  - Demonstration of product comparability is more difficult
  - Changes in manufacturing and scale-up can impede approval

Post-translational modifications

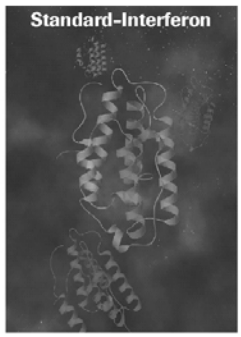
In vivo modifications:

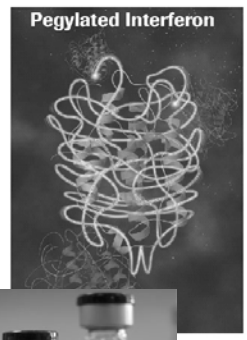
- Glycosylation
- Proteolysis
- Acylation
- Sulfation
- many others

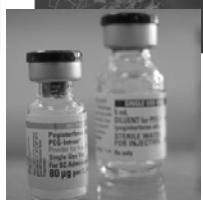


Intentional Modifications

- PEGylation
- Proteolysis
- Conjugation
- Radiolabeling

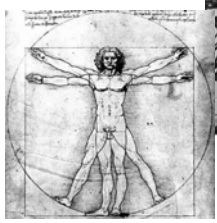


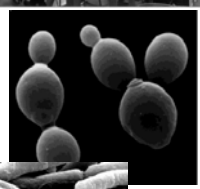


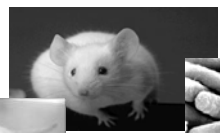


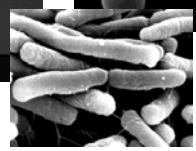
Diverse Sources

Humans
Human cell culture
Mice
Rodent cell culture
E. coli
Yeast
Transgenics







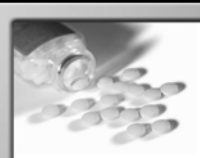


Biologics - Unique Aspects I.

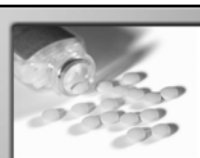
- Source material for biologics
  - Potential for transmission of adventitious agents
    - Bacteria, mycoplasma, fungi, viruses, TSE agents
  - Need for in-process controls, validation
- Heat Sensitive & susceptible to microbial contamination
  - Controlled temperature during production
  - Aseptic processing throughout
  - Cannot terminally sterilize
- Formulations
  - Majority parenteral
  - Issues with concentration, multi-use vials

Biologics - Unique Aspects II.

- Pharmacokinetics
  - Not well established
  - May not be able to measure
- Potential immunogenicity
  - Desirable in vaccine strategies
  - Unwanted effects in other settings (single- or chronic-dosing)
    - Altered PK
    - Allergic, serum-sickness reactions
    - Cross reactivity to normal, essential protein
  - Limitations of non-clinical studies
    - Species-specific antibody development

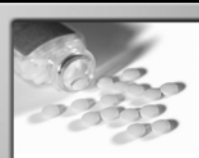


What Biologics are Regulated by CDER?



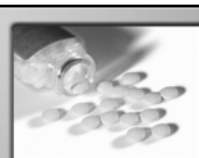
Therapeutic Biological Products (TBP)

- Monoclonal antibodies for *in vivo* use
- Proteins intended for therapeutic use that are extracted from plants, animals or microorganisms, including recombinant versions of these products (except clotting factors)
- Other non-vaccine therapeutic immunomodulators



Therapeutic Biologicals -Examples

- Cytokines
  - Interferons - α, β, γ,
  - Interleukins - IL2, IL11
- Hematopoietic growth factors
  - Erythropoietins
  - CSFs
- Enzymes
  - thrombolytics (e.g. streptokinase, TPA)
  - Aldurazyme
  - Rasburicase



Therapeutic Biologicals - cont'd

- Monoclonal antibodies
  - Anti-IL2R (Basiliximab)
  - Anti-IgE (Omalizumab)
- Fusion proteins
  - TNFR linked to Fc portion of human IgG (Etanercept)
  - LFA3TIP fused human IgG1 heavy chain (Alefacept)

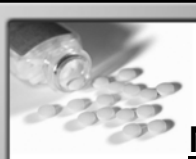
Oncology

- Herceptin (trastuzumab) breast cancer, ushers in new area of highly targeted therapy
- Rituxan (rituximab) targets some lymphomas
- Zevalin (ibritumomab tiuxetan), first monoclonal antibody targeted radiotherapy
- Campath (alemtuzumab) for CML
- Avastin (Bavacuzimab) first line metastatic colorectal Cancer
- Erbitux (Cetuximab) recurrent colorectal Cancer

- Hematopoietic support
  - Several CSFs (Neulasta: PEG-G-CSF) support WBC production and decrease infection risk
  - Several EPOs (Aranesp: darbepoietin alfa) avoid blood transfusion in anemia from cancer chemotherapy, renal failure
- Cardiology
  - Fibrinolytics reduce mortality of acute MI
  - ReoPro (abciximab) anti-platelet agent prevents abrupt coronary closure after coronary procedures.
- Pulmonary
  - Omalizumab (anti-IgE) – asthma
  - Pulmozyme (DNAase) - CF

- **Infectious Disease**
  - Xigris (rhAPC): first therapy targeting severe sepsis, reduces mortality in high risk patients
  - IFN alfas (PEG-IFN alpha / ribavirin): chronic Hepatitis C
  - Synagis (ab to RSV): prevent RSV infections
- **Dermatology**
  - Enbrel, Alefacept (anti-LFA3), Raptiva (anti-CD11a) – psoriasis
  - Regranex (PDGF) – diabetic ulcers
  - Palifermin – mucositis following myelotoxic therapy
- **Hereditary deficiencies**
  - IFN gamma for osteopetrosis
  - Enzyme replacement for inborn errors (Fabry, MPS 1)

- Arthritis
  - Remicade (anti-TNF) – RA, AS, Psoriatic
  - Enbrel (Fc TNF-R) - RA, JRA, AS, Psoriatic Arthritis
  - Anakinra (IL-1RA) - RA
  - Humira (anti-TNF) - RA
- Neurology
  - IFN betas: Multiple sclerosis
  - tPA for stroke
  - Bo-tox for N-M disorders



Biological Products
Not regulated by CDER !!!

- Cellular products
- Gene therapy products
- Vaccines
- Allergenic extracts
- Antitoxins
- Blood, blood components, and plasma-derived products.

Note: These Biological Products are Regulated by the Center for Biologics Evaluation and Research (CBER)

Regulation of Biologics

NDA versus BLA

- There are many similarities (e.g. regulations, guidance documents, PDUFA)
- Most differences are due to type of product, not due to which FDA Center regulates the product

	Law	Regulation	PDUFA
IND	FD&C Act	25, 50s, 211, 312	Same
BLA	PHS Act FD&C Act	25, 201-2, 207, 211, 600s	Same
NDA	FD&C Act	25, 201-2, 207, 211, 314	Same
Post BLA	PHS Act FD&C Act	201-2, 211, 600s	Same
Post NDA	FD&C Act	25, 201-2, 207, 211, 314	Same

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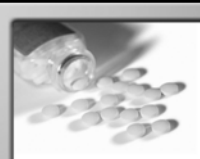
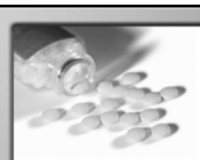


How Does a Biologic Get Licensed?



Current Laws

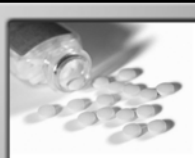
- Public Health Service Act (1944)
  - Section 351 -- Licensure of biological establishments and products
- FFD&C Act (1938, 1962)
  - Interprets that “biological products” are also “drugs”
    - The FFD&CA applies to a biological product, except no application required under section 505.

PHS Act
(As Amended by FDAMA)

- The Secretary shall approve a biologics license application:
  - On the basis of a demonstration that
    - Product is safe, pure and potent
    - The facility(ies) meet standards designed to assure that it continues to be safe, pure, and potent
  - If the applicant consents to the inspection of the facility(ies)
  - Each package of biological product must bear the U.S. license number

Regulations

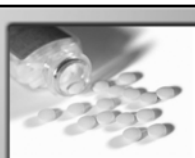
- 21 CFR 601.2(d): “Approval of a biologics license application or issuance of a biologics license shall constitute a determination that the establishment(s) and the product meet applicable requirements to ensure the continued safety, purity, and potency of such products” including but not limited to GMPs.
- 21 CFR 600.3(n): Standards means specifications and procedures applicable to an establishment or to the manufacture or release of products, which are prescribed in this subchapter or established in the biologics license application designed to insure the continued safety, purity, and potency of such products.



Standards

- CFR Standards for Biologics include:
  - (p) "**safety** means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time."
  - (r) "**Purity** means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances."
  - (s) "**potency** is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."

See 21 CFR 600.3 and Part 610



A Biologics Subset

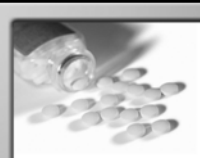
- "Specified" (definition from 21 CFR 601.2):
  - Therapeutic recombinant DNA-derived products
  - Monoclonal antibody products for in vivo use
  - Therapeutic synthetic peptide products of 40 amino acids or less
  - Therapeutic DNA plasmid products
- Most CDER-regulated Biologics are "specified"

"Specified" Biological Products

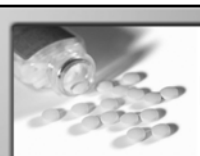
- Certain 600s regulations to do not apply (per 601.2(c)):
  - Exempt from General Safety Testing (21 CFR 610.11)
  - Package labeling requirements harmonized with NDA regulations (e.g. exempt from 21 CFR 610.62 re: prominence)
- Complete Establishment Description Section of BLA not required

Approval Letter

"This letter hereby issues Department of Health and Human Services U.S. License No. XXXX to _____ in accordance with the provisions of Section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards."

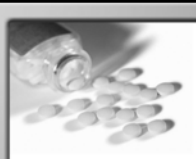


What Happens After Approval?



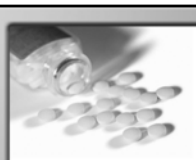
BLA Post-Approval Requirements

- Required annual reports:
  - PMC status (601.70)
- Other required submissions:
  - Adverse Events (600.80)
  - Distribution summary (600.81)
  - Biologic Deviation Reports (600.14)
  - Advertising and Promotional Labeling
- Periodic cGMP inspections



Changes to be Reported (21CFR 601.12)

- Manufacturing Changes
  - Pre-Approval Supplements (PAS)
  - 30-day Supplements (CBE30)
  - Annual Reports – only if reportable changes
- Labeling Changes
  - Pre-Approval Supplements
  - Changes Being Effected (CBE) Supplements
  - Annual Reports – only if reportable changes



NDA and BLA Similarities & Differences

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NDA	FD&C Act	25, 201-2, 207, 211, 314	Same
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Post NDA	FD&C Act	25, 201-2, 207, 211, 314	Same

Specific Similarities Include:

- IND regulations, Fast Track designation, Special Protocol Assessment (SPA)
- Financial Disclosure, CTD format
- Labeling and Advertising (21CFR 201-202)
- Pediatric study requirements and waivers
- Accelerated Approval

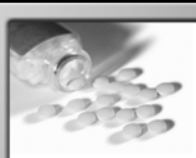
CDER Forum for International Drug Regulatory Authorities

Unique to NDAs:

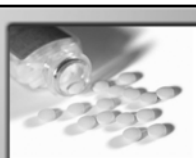
- Patent Exclusivity (thus, generics, 505b2, & Orange Book)
- Pediatric Exclusivity (written requests)
- NDA Field Copies
- Regulations more detailed re: NDA content; filing criteria

Unique to BLAs:

- U.S. License
  - Product and facility must meet “standards” prior to license issuance
  - Review includes
    - Application review
    - Facility inspection (Pre-approval, review members participate)
    - Method validation complete
    - Compliance check
  - Cooperative manufacturing arrangements permitted
    - Divided, Shared, Contract
- FDA “official” release (21 CFR 610.2) of each product lot (at discretion of FDA)
- Container & Pkg. Label requirements

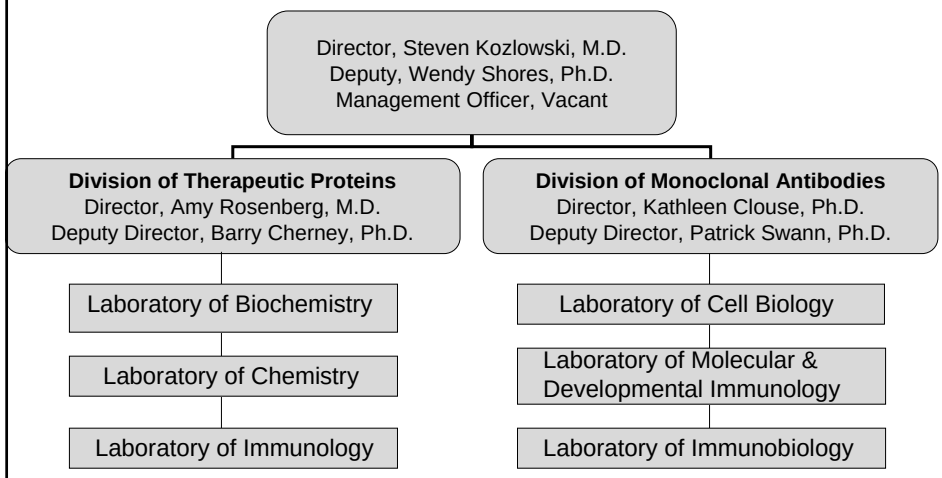


CDER Structure



CDER Forum for International Drug Regulatory Authorities

Office of Biotechnology Products



Reference Slides

Internet Resources

- Therapeutic Biological Products regulated in CDER
  http://www.fda.gov/oc/combination/transfer.html
- FDA intercenter Agreements
  www.fda.gov/oc/combination/intercenter.html
- Biologics Centennial & CBER History
  http://www.fda.gov/cber/inside/centennial.htm
- CDER history
  http://www.fda.gov/cder/about/history/Histext.htm

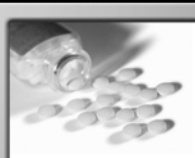
CDER Forum for International Drug Regulatory Authorities

The 600s = BLA regulations

- 21 CFR Part 600 -- Biological Products: general
  - Subpart A: Definitions
  - Subpart B: Establishment Standards
    - Personnel
    - Facility, equipment, animals
    - Retention samples
    - Biological Product Deviations
  - Subpart C Establishment Inspections
  - Subpart D Reporting of Adverse Events
    - Postmarketing reporting
    - Distribution reports

The 600s (cont.)

- 21 CFR Part 601 – Licensing
  - Applications
  - Issuance of license
  - Revocation
  - Suspension
  - Changes to be reported (601.12)
  - Accelerated Approval (601 Subpart E)
  - Confidentiality of data
  - Annual Reports of postmarketing studies (601.70)



The 600s (cont.)

- 21 CFR Part 610 -- General Biological Product Standards
  - Release
    - 610.1 – lot release (manufacturer)
    - 610.2 – Samples for “Official” FDA testing and release
  - Testing
    - Potency
    - General Safety
    - Sterility
    - Purity (including moisture)
    - Mycoplasma
  - Dating Periods
  - Labeling